IN THE UNITED STATES PATENT AND TRADEMARK OFFICE.

In re Application of Keith)
Serial Number: 07/542,149) Art Unit: 184
Filed: June 22, 1990) Examiner: C. Low

For: PERTUSSIS TOXIN GENE: CLONING AND EXPRESSION

#7

PETITION UNDER 37 C.F.R. 1.144

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

The Commissioner is respectfully requested to review a restriction requirement made in application 07/542,149, filed on June 22, 1990. The formal written restriction requirement was mailed April 1, 1991. The restriction requirement was traversed by applicant in a response filed June 3, 1991. The Examiner made the restriction requirement final in the subsequent Office Action dated June 19, 1991.

It is respectfully submitted that the Office failed to define a proper basis of distinctness between Invention I, drawn to cloned genes encoding a mutant pertussis toxin, and Invention II, drawn to the polypeptides constituting mutant pertussis toxins. The Examiner stated:

> "The inventions are distinct, each from the other because of the following reasons:
> The inventions of Group I and II are capable of separate manufacture, use, and have different properties as claimed and are patentably distinct. The pertussis

gene of Group I can be obtained by traditional chemical synthesis and is useful as a genetic probe. The polypeptides of Group II can be obtained by traditional solid phase chemical synthesis and thus do not have to be obtained via a process requiring recombinant DNA or any other biological route to obtaining the protein."

While applicant acknowledges the instant polypeptides and cloned gene encoding same clearly are related inventions, applicant traverses each of the above reasons for distinctness as not appropriate for the relationship that exists between Invention groups I and II. The cloned genes of Invention Group I and the polypeptides of Invention Group II are related through the information content encoded by the nucleotide sequences of the cloned genes. Possession of the cloned gene enables one skilled in the genetic engineering art to make the polypeptide via the biological/cellular processes of gene/DNA transcription and RNA translation. Within this synthetic process, DNA is not an intermediate of an intermediate-final product relationship. In chemical/biological intermediate-final product relationships, the intermediate loses its identity (i.e., is consumed) in the conversion process to the final product. See MPEP 806.04(b). By contrast, DNA is not changed or destroyed in the biological processes which transcribe and translate its genetic information into the structural information content of the polypeptide.

The cloned DNA, however, is a necessary starting material for the manufacture of the polypeptides. In this regard, the

Examiner's statement above "that the polypeptides of Group II can be obtained by traditional solid phase chemical synthesis" is not correct. In order to perform solid phase chemical synthesis of the instant mutant polypeptides, the skilled artisan first must know their amino acid sequence. The amino acid sequences of these polypeptides, however, are not disclosed. While methods for determining amino acid sequence of proteins exist in the art, these methods require isolated/pure protein preparations. However, the person skilled in this art could not isolate and purify the instantly claimed polypeptides because they normally do not exist in nature. These polypeptides came into existence only through the genetic engineering endeavors of applicant. Consequently, expression of the cloned genes of Invention Group I is the only mechanism to derive the new polypeptides of the instant invention for the purpose of sequencing.

In view of the above discussion, the Examiner's allegations about chemical synthesis of the polypeptides begs the question regarding the fundamental informational relationship between novel genes and their corresponding protein expression products. One can not elucidate sequence information content of a genetically derived new protein without first having utilized the informational content of the gene to synthesize the protein. This statement is so inherently intuitive that, when formally stated, it appears

circularly redundant. Yet, the Examiner proposes to sever this intuitive relationship and divorce an non-sequenced, novel, and genetically engineered polypeptide from the cloned gene possessing the information for synthesis of that polypeptide. There is an informational unity that inseparably connects applicant's new proteins to its encoding genetic elements, and applicant respectfully requests this unity not be artificially divided through the instant restriction requirement.

Within the sphere of MPEP 806.05-806.05(i), the only alternative explanation for the Examiner's allegation "That the polypeptides of Group II can be obtained by traditional solid phase chemical synthesis and thus do not have to be obtained via a process requiring recombinant DNA or any other biological route to obtaining the protein." is that the Examiner has confused the true relationship between applicant's invention groups with the distinctness relationship of a process of making and product made [per MPEP 806.05(f)]. Clearly, there are no method of making claims and this distinctness category is not appropriate for instant Invention Groups I and II. Even assuming arguendo that applicant's invention groups were perceived as being analogous to method of making and product made, the distinctness requirement would not be satisfied for the reasons set forth supra.

The Examiner's next incorrect allegation is that the cloned

gene of Invention Group I "is useful as a genetic probe.". It is assumed the Examiner means probes for hybridization protocols used to assay test genomes for DNA sequences corresponding to the instantly claimed DNA. This is illogical. Applicant created these novel genes by site-specific mutagenesis. They do not exist in the sequences of the corresponding genes of Bordetella pertussis. It is respectfully submitted that one skilled in this art would not use probes to assay for gene sequences that are non-exist outside of applicant's claimed gene constructs. It appears the Examiner has seized, ad hoc, upon a generalized utility applicable to some cloned genes without attention to the particular fact situation of the instant claims, which renders inappropriate this hypothetical utility.

It is noted that the Examiner did not present the distinctness rationale within the framework of Form Paragraphs corresponding to the distinctness categories enumerated in MPEP 806.05 to 806.05(i). Review of this section on the MPEP indicates the only distinctness category that addresses different uses is MPEP 806.05(h); directed to inventions related as product and method of use. Clearly, this distinctness category is not appropriate for the relationship between instant Invention Groups I and II. Consequently, the Examiner's assertions regarding different uses can not find justification within the accepted guidelines of MPEP 806.05(h).

The final basis for distinctness proffered by the Examiner stated that the inventions of Groups I and II "have different properties as claimed". This is not a recognized and valid distinctness criteria upon which to base a restriction requirement. It is submitted that all claims must "have different properties" or they would be subject to criticism as being duplicative or not further limiting a prior claim. The Examiner's conclusion that Groups I and II "are patentably distinct" requires a basis within the guidelines of MPEP 806.05. The bases provided by the Examiner are factually/conceptually incorrect as discussed supra, and/or correspond to inappropriate distinctness categories within MPEP 806.05; i.e., product and process of making or process of use. Consequently, the Examiner erred in applying the above distinctness bases to applicant's related inventions.

In making the restriction requirement final in the Office Action of June 19, 1991, the Examiner appears to have misinterpreted applicant's traverse. The Examiner states:

> "The traversal is on the ground(s) that the mutant pertussis toxin proteins of Group II are related and that they are not related (see page 4 of the response to the restriction) is not convincing nor have any reasons been presented showing that a polypeptide can be directly used to produce a DNA or address. Here, and as argued in the response, the protein and the DNA are chemically distinct compositions."

Applicant does not assert the instant invention groups are unrelated. Applicant merely submits that they are not related in

the manner alleged by the Examiner or according to the distinctness categories implicit from the restriction requirement.

The second part of the Examiner's rebuttal statement is also confusing. The examiner seems to have inverted the "not required to make" basis for distinctness in the original restriction requirement, which alleged that the DNA of Invention Group I was not required to make the protein of Invention Group II. The proper informational relationship between the DNA and protein of the instantly claimed invention was described supra. The flow of information in this relationship is one way. The sequence of nucleotides within DNA is not effected by somatic alterations in the primary amino acid sequence in a molecule of the corresponding protein. Were such a backward flow of information to occur, it would result in inheritance of acquired traits. The assertion that applicant's traverse to the restriction requirement is not convincing because it did not provide evidence/reasons for such a genetic nonsequitar is repugnant to the genetic art. Regarding the final portion of the above rebuttal statement, applicant's review of the MPEP fails to find a valid basis for restriction between related inventions predicated on "the compositions are chemically distinct". The indication that the instant invention groups are "chemically distinct" simply is not sufficient justification to require restriction between two related

inventions. In this regard, the "chemically distinct" criteria for restriction is subject to the same criticism as the Examiner's previous statement that instant Invention Groups I and II should be restricted because DNA and polypeptides have "different properties as claimed".

The remainder of the June 6, 1991 rebuttal of applicant's traversal of the restriction requirement relates to the Examiner's justification for establishing a burden on the Office. The Examiner states: "Moreover, any manual or "on line" search of the available patents and published nonpatent literature such as recognized peer reviewed journals would not be so coextensive as to result in a complete and thorough search for the polypeptides when a search is conducted for DNA or when conducted in the reverse order;--". Again, the Examiner appears to be in error. Review of the Keith et al patent 4,883,761 and Locht et al. 1986 Science article (i.e., the two full length references applied as art against the instant claims) disclose both nucleotide sequence and predicted corresponding amino acid sequence. Indeed, it is common in this art for references to apply the genetic code and knowledge about open reading frames to make predictions of the amino acid sequence of a protein based upon the nucleotide sequence of its cloned gene. It is understood that the PTO classification system classifies genes in the class/subclass corresponding to DNA. This

relates back to the old practice of classifying DNA as a chemical (i.e, a carbohydrate). Applicant is not claiming DNA, the chemical. Rather, applicant is claiming cloned genes composed of DNA. The cloned gene inherently possesses sequence information as discussed previously, which transcends its evaluation as a carbohydrate derivative. As indicated supra, it is this sequence-related informational content which unifies the cloned gene and protein as a single inventive concept. Patent and journal art directed to this informational aspect of genes and proteins (exemplified by the art cited against the claims in the Office Action on the Merits) do not make the artificial distinction advanced by the Examiner. It is respectfully submitted that a complete and thorough search of claims drawn to cloned genes, whose utility includes expression of a polypeptide, should be coextensive in content with a search of the polypeptide, per se.

Regardless, proper restriction practice additionally requires that related inventions be patentably distinct. MPEP 803 sets forth this dual requirement for restriction, and directs the reader to MPEP 806.05-806.05(i) which defines the accepted criteria for restriction between related inventions. The MPEP at Section 808.02 again makes clear the distinctness criteria required for proper restriction when it states: "Where the related inventions as claimed are shown to be distinct under the criteria of >MPEP<

Sections 806.05(c-i),---". The Examiner has failed to set forth a category or criteria for restriction in concert with MPEP 806.05. Furthermore, the distinctness argument proffered by the Examiner falling outside the guidelines of MPEP 806.05 have been discussed above, and shown to be erroneous and/or not applicable to the instantly claimed invention.

For all the above considerations, it is submitted that the Examiner did not make a proper restriction requirement. Withdrawal of the restriction requirement is in order, and the claims of Invention Groups I and II should be rejoined. For this purpose, the Commissioner is respectfully requested to grant this petition.

Should the Commissioner have any questions or comments regarding the present request for reconsideration of the Examiner's restriction requirement, he is respectfully requested to contact Robert Benson at (301) 496-7056.

Please charge any fees or credit any overpayment pursuant to 37 C.F.R. 1.16 or 1.17 to Deposit Account Number 14-1052.

Respectfully submitted,

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Date July 15, 1991